

AB INITIO STUDIES ON HEXAVALENT PHOSPHORUS COMPOUNDS

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ABSTRACT

The reaction of some organophosphorus compounds with cholinesterase is thought to proceed by nucleophilic substitution through a pentacoordinate trigonal bipyramidal structure. Recently, Robert Holmes suggested that a hexacoordinate species might be involved instead. Hartree-Fock calculations were performed on a series of hexavalent phosphorus compounds in which a nitrogen atom provided both electrons for the sixth bond — thereby forming an octahedral complex. In general, electron-withdrawing groups on the phosphorus atom increased the strength of the coordinate covalent bond between the nitrogen and phosphorus atoms. When the hexavalent phosphorus species was constructed by addition of ammonia and hydroxide to a phosphonate, the P-N distance was over 4 Å. This weak interaction is inconsistent with the hypothesis that nitrogen ligands accelerate the rate of hydrolysis by forming a hexavalent transition.

INTRODUCTION

When a neural impulse, traveling down the axon from the nerve body, reaches the nerve terminal, acetylcholine is released, which diffuses across the synapse between the two neurons. The acetylcholine molecule binds to the cholinergic receptor on the postsynaptic neuron and stimulates a new neural response.¹ Acetylcholine dissociates from the receptor and is hydrolyzed into acetate and choline by a reaction catalyzed by acetylcholinesterase. Because

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neither product is capable of stimulating the cholinergic receptor subsequent stimulation does not occur. Nerve agents inhibit the acetylcholinesterase, irreversibly. Inhibition occurs by the formation of a covalent bond with serine in the active site of protein, thereby blocking the active site and preventing the binding of the acetylcholine molecule.^{2,3} Inhibition of the enzyme leads to uncontrolled accumulation of acetylcholine at the synapse and continued stimulation until the neurons become depolarized.

The reaction leading to inhibition occurs by nucleophilic attack of the serine on the organophosphorus ester. For several years, the consensus has been that the reaction proceeded through a pentavalent transition structure. Recently, Robert Holmes postulated that some enzyme reactions, specifically, the hydrolysis of cyclic AMP by phosphodiesterases, might progress through a hexavalent transition or intermediate.^{4,5} This hexavalent species is formed from the five traditional ligands and a coordination complex, with neighboring amino groups in the active site of the enzyme. This coordination complex is formed by the donation of two electrons from a Lewis base to the phosphorus atom.

Most of the research on phosphorus compounds has been on trivalent and pentavalent species.⁶ Although there has been some interest in hexavalent phosphorus, most of the activity has been empirical with relatively little theoretical work on the nature of molecular bonding. The first step in testing the hexavalent transition hypothesis of Holmes is a quantum chemistry study of various hexavalent phosphorus compounds and ions to determine the effects of the sixth ligand on the geometry of the molecule and electronic structure of the central phosphorus atom.

METHODS

All calculations were performed with Gaussian 94 using the Berny optimization routine and the default parameters. Input matrix was created with Gaussview 2.0. Quantum calculations were run at the restricted Hartree Fock level of theory with the following basis sets: 3-21G, 6-31G, 6-31G*, and 6-31+G*. Frequency calculations were performed on all optimized structures to confirm that the stationary points were minima. Calculations were performed on isolated molecules (gas phase) without any solvation models. Output was visualized with Gaussview.

RESULTS

Table #1 delineates the bond lengths of small fluorophosphorus compounds. PF_3 had a trigonal symmetry with the lone pair at the apex. The F–P–F bond angles were 96° for the 3-21G basis set, 96° for the 6-31G basis set, 97° for the 6-31G* basis set, and 97° for the 6-31+G* basis set. These angles compare with the experimental value of 98° .

The PF_4^+ molecule was tetrahedral (F–P–F bond angle= 109.5°) with all basis sets. In contrast, the PF_4^- anion must accommodate a lone pair of electrons and therefore cannot have tetrahedral symmetry. The C_2V structure is a pseudo trigonal bipyrimid having a lone pair of electrons in one of the equatorial positions rather than a fifth ligand. The results from x-ray

crystallography for $\text{N}(\text{CH}_3)_4\text{PF}_4$ were not conclusive.⁷ The $\text{N}(\text{CH}_3)_4^+$ cations were well ordered; however there was considerable disorder in the PF_4^- anions. The authors used a disorder model to resolve the discrepancies and with the assistance of density functional theory obtained the most probable bond lengths indicated in Table 1.

The PF_5 molecule had trigonal bipyramidal geometry, where the axial bond lengths were longer than the equatorial bond lengths. The difference between the axial and equatorial bond lengths increase as the basis set increases.

The bond lengths in the PF_6^- anion depend to some extent upon the cation. Two are listed in Table 1. All have an octahedral geometry with the obligate 90° bond angles. In the clathrate of hexafluorophosphoric acid, the PF_6^- anion occupies two distinct sites within the cavity.⁸ Resolution of the diffraction pattern gave P—F bond lengths of 1.601 & 1.568 Å. These compare with 1.609 Å with the 6-31+G* basis set. In this study, calculated bond lengths decreased as the size of the basis set increased.

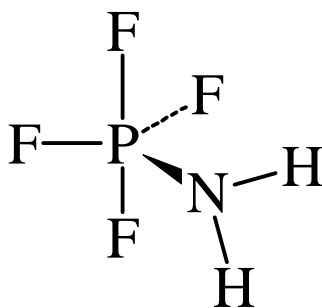
TABLE 1. Bond Lengths of Phosphorus Fluorides
(in Å).

Basis Set	PF_3	PF_4^-	PF_4^+	PF_5	PF_6^-
	Pyramidal	Pseudo Trigonal Bipyramidal	Tetrahedral	Trigonal Bipyramidal	Octahedral
3-21G	1.609	Axial 1.724 Equatorial 1.642	1.548	Axial- 1.604 Equatorial- 1.581	1.625
6-31G	1.663	Axial 1.798 Equatorial 1.695	1.598	Axial-1.655 Equatorial- 1.633	1.680
6-31G*	1.564	Axial 1.719 Equatorial 1.610	1.479	Axial- 1.568 Equatorial- 1.535	1.606
6-31+G*	1.569	Axial 1.746 Equatorial 1.609	1.479	Axial- 1.572 Equatorial- 1.535	1.609
Empirical	1.570	Axial 1.74 ⁷ Equatorial 1.60	N/A	Axial- 1.577 ⁹ Equatorial- 1.534	1.56 ¹⁰ 1.601 &1.568 ⁸

Based on the results produced with the 4 basis sets for the PF_3 and PF_5 molecules, it appears that the largest basis set (6-31+G*) generates values closest to the empirical. In addition to providing a double zeta number of basis functions, this set contains d orbitals on the non hydrogen atoms. The diffuse functions are important for the negatively charged species in which greater electron density may be present in areas more distant from the nucleus. Results with the smallest basis set (3-21G) are included for comparison.

The bond lengths of the PF_4NH_2 molecule calculated with the 3-21G and the 6-31+G* basis sets are indicated in Table 2. The amine moiety occupies one of the equatorial positions in the trigonal bipyramid. The axial fluorines have a bond length of 1.599 Å, which is slightly longer than those in the PF_5 molecule described in Table 1. The equatorial P—F bonds (1.590 Å) are also shorter than in PF_5 . The P—N bond length determined with the larger basis set (6-31G*) is 1.614 Å. In contrast, the small 3-21G basis set gave a longer bond length of 1.642 Å.

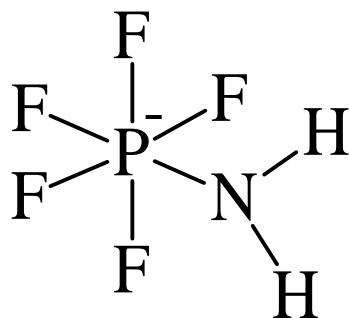
TABLE 2. Calculated Bond lengths (Angstroms) for PF_4NH_2 .



(Bond lengths in Å)

Basis Set	P—F	P—N	N—H
3-21G	Equatorial 1.590 Axial 1.624	1.642	0.996
6-31+G*	Equatorial 1.546 Axial 1.599	1.614	0.995

Addition of another fluoride ion produces the PF_5NH_2^- anion. The geometry of this ion is indicated in Table 3. The bond lengths in this octahedral structure are considerably longer than the PF_4NH_2 molecule described in Table 2. The P—N bond at 1.735 Å (6-31+G*) is about 1.2 Å longer than the corresponding bond.

TABLE 3. Calculated Bond lengths of PF_5NH_2^- .

(Bond lengths in Å)

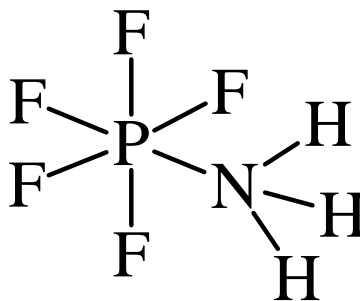
Basis Set	P—F	P—N	N—H
3-21G	Adjacent 1.640 Trans 1.647	1.722	0.994
6-31+G*	Adjacent 1.627 Trans 1.644	1.735	1.000

Addition of a proton to the amine produces an uncharged species also having octahedral geometry (Table 4). This molecule can be considered a coordination complex with the NH_3 molecule serving as a Lewis base and the PF_5 molecule as a Lewis acid. It is not surprising that the P—N bond length is longer (1.919 Å for the 6-31+G*) than in the anion. As would be expected, the P—F bonds shorten to 1.594 Å for the 4 fluorines adjacent to the nitrogen. In the neutral molecule, the trans P—F bond is shorter than the adjacent; whereas the opposite occurs in the PF_5NH_2^- anion.

The inhibition of acetylcholine by organophosphorus nerve agents occurs as a result of nucleophilic substitution of the fluorine by the serine moiety in the active site of the enzyme. As indicated in the introduction, it is generally believed that this reaction proceeds through a pentavalent trigonal bipyramid intermediate or transition structure.

Table 5 contains bond lengths of a similar intermediate resulting from the nucleophilic attack of OH^- upon $\text{CH}_3\text{P}(\text{O})\text{FOCH}_3$. The optimized geometries were slightly different for the two basis sets. With the smaller 3-21G, the hydroxyl occupied one of the equatorial positions and the phosphoryl oxygen was axial. The larger 6-31+G*, which contains diffuse functions produced a more reasonable geometry in which the nucleophile (OH) and the leaving group (F) occupied the two axial positions. As would be expected, the single bond P—OH was considerably longer than the polar phosphoryl bond, which is frequently written as $\text{P}=\text{O}$. The axial P—F bond is also longer than analogous bonds indicated in Tables 1 and 2.

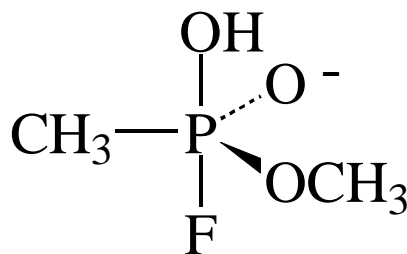
TABLE 4. Calculated Bond Lengths of PH_5NH_3 Molecule.



(Bond lengths in Å)

Basis Set	P–F	P–N	N–H
3-21G	Adjacent 1.616 Trans 1.593	1.946	1.012
6-31+G*	Adjacent 1.594 Trans 1.558	1.919	1.006

TABLE 5. Calculated Bond Lengths of $\text{PO}(\text{CH}_3)\text{F}(\text{OH})\text{OCH}_3^-$.

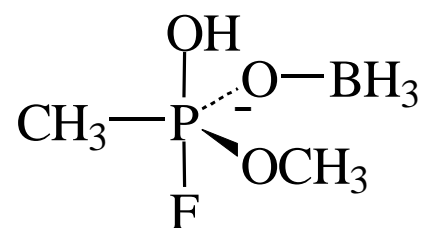


(Bond lengths in Å)

Basis Set	P–F	P–C(H)	P–O(C)	P–O(H)	P–O
3-21G	1.762	1.838	1.644	1.645	1.530
6-31+G*	1.743	1.847	1.697	1.731	1.558

Reducing the electron density in the intermediate by adding a Lewis Base (BH_3) to the phosphoryl oxygen shortens the bond lengths for all the other atoms (Table 6). Addition of the BH_3 group, lengthens the $\text{P}=\text{O}$ bond from 1.558 Å to 1.824 Å. Electrons are shifted from the $\text{P}=\text{O}$ bond to form the $\text{O}-\text{B}$ bond — thereby weakening and lengthening the $\text{P}=\text{O}$ bond. The $\text{P}-\text{F}$ bond shortens from 1.74 Å to 1.58 Å — about the same as that in the uncharged PF_5 molecule

TABLE 6. Calculated Bond lengths for the Pentavalent/ BH_3 complex.

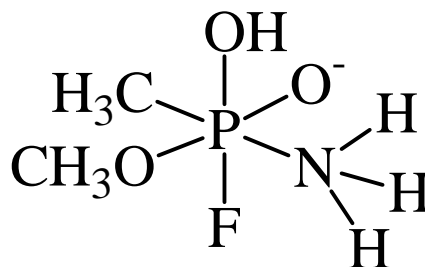


(Bond lengths in Å)

Basis Set	P-F	P-C(H)	P-O(C)	P-O(H)	P-O(B)
3-21G	1.634	1.726	1.667	1.657	1.843
6-31+G*	1.580	1.745	1.621	1.607	1.824

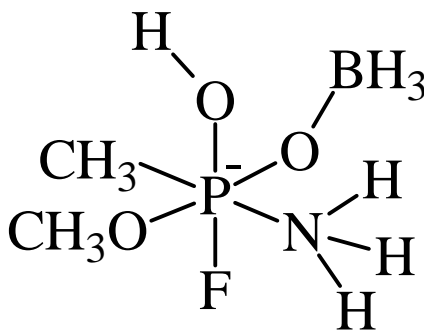
Addition of NH_3 to the pentavalent structures indicated in Table 5 and 6 produce analogous hexavalent ions whose bond lengths are listed in Tables 7 and 8. As indicated in Table 7, the $\text{P}-\text{N}$ bond distance is over 4 Å. At this distance, essentially no electron interaction occurs between the nitrogen and the phosphorus. Addition of the BH_3 to the phosphoryl oxygen shortened the $\text{P}-\text{C}$, $\text{P}-\text{OH}$, and $\text{P}-\text{C}$ bonds ($\text{P}-\text{F}$ bond lengthened) but had little effect on the phosphorus-nitrogen bond distance.

TABLE 7. Bond Lengths of Octahedral Complex.



(Bond lengths in Å)

Basis Set	P-F	P-O(C)	P-O(H)	P-O	P-C(H)	P-N(H)
3-21G	1.701	1.665	1.730	1.492	1.846	3.252
6-31+G*	1.717	1.633	1.752	1.498	1.834	4.101

TABLE 8. Bond Lengths of Octahedral Complex with BH₃.

(Bond lengths in Å)

Basis Set	P-F	P-O(C)	P-O(H)	P-O(B)	P-C(H)	P-N(H)	O-B
3-21G	1.756	1.663	1.693	1.600	1.834	3.594	1.220
6-31+G*	1.742	1.619	1.665	1.534	1.826	4.284	1.224

The Mulliken partial charges on the individual atoms for the penta and hexavalent phosphorus compounds and ions are indicated in Table 9. For PF_6^- , the partial charge on phosphorus is 4.43 with negative charges evenly distributed among the six fluorines. Replacement of one of the fluorines with nitrogen adds electron density to the system and reduces the phosphorus charge to 3.92. Addition of H^+ to the PF_5NH_2^- anion creating a neutral molecule has little effect on the electron density of any individual atom because the electrons needed to form the new N—H bond are averaged over the entire molecule.

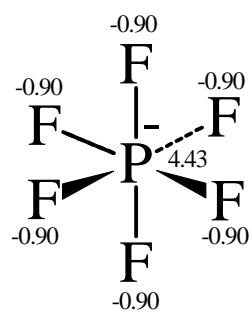
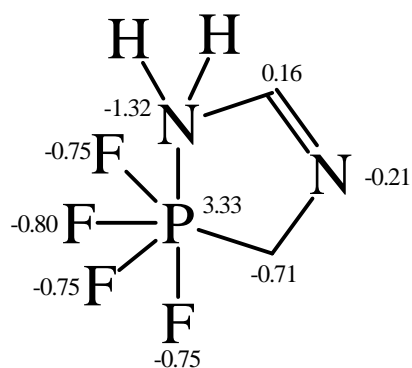
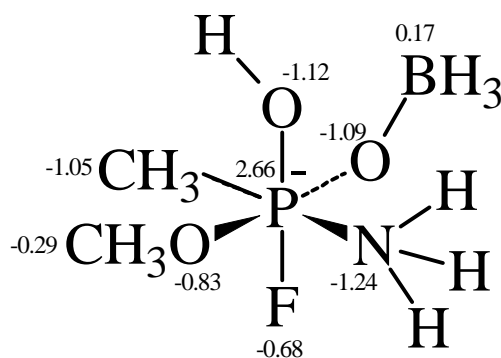
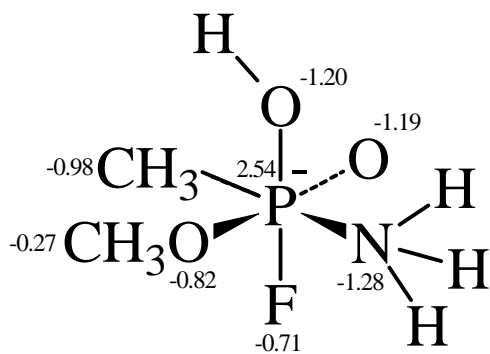
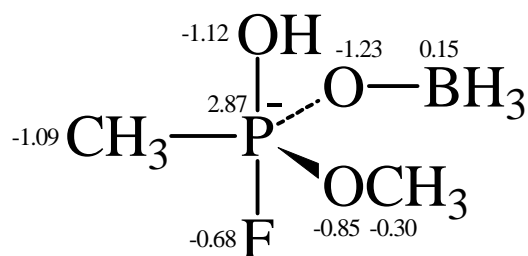
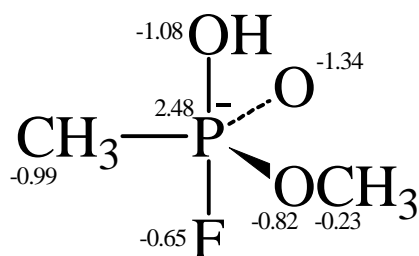
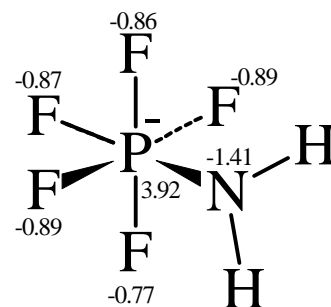
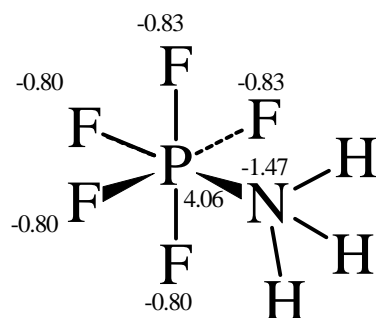
The pentavalent anion formed by addition of OH^- to methyl methylphosphonofluoridate has a positive charge of 2.48 on the phosphorus. Addition of the Lewis acid BH_3 causes a slight reduction in the negative charge on the phosphoryl oxygen (electrons originally on the oxygen form the O—B bond) and creates additional positive charge on the phosphorus (i.e., $2.48 \rightarrow 2.87$).

Addition of NH_3 to the pentavalent phosphonate anion has only a small effect on partial charges. The changes may be the result of a different geometry around the phosphorus rather than electronic contributions by the ammonia molecule. Addition of BH_3 to the phosphoryl oxygen in the hexavalent system induced the same effects qualitatively as in the pentavalent; however, the magnitude of the changes in electron density was considerably less. The partial negative charge on the nitrogen in all P— NH_3 systems with hexavalent phosphorus was in the range of -1.3 ± 0.1 . The various substituents on the phosphorus had little effect. As a corollary, the NH_3 moiety exerted little influence on the partial charge on the phosphorus and the other substituents.

CONCLUSIONS

Hexavalent phosphorus compounds formed by the addition of ammonia to PF_5 are stable species having P—N bonds about 1.9 Å in length. These bonds are longer than traditional P—N bonds in tetravalent and pentavalent phosphorus compounds. The hexavalent phosphorus nitrogen compounds are sufficiently stable to be synthesized and crystallized. In contrast, quantum calculations at the Hartree-Fock level of theory using double zeta quality basis sets containing both polarization and diffuse functions provide no evidence of a complex between an anionic phosphonic intermediate and ammonia. Upon optimization, the nitrogen separated from the phosphorus. Attempts to stabilize the complex by adding a Lewis base (BH_3) to the phosphoryl complex did not increase the interaction between the phosphorus and nitrogen. These calculations are inconsistent with the premise that nucleophilic substitution of phosphorus fluoridates by serine proceeds through a hexavalent transient in which the sixth bond results from a coordination complex between the phosphonate and an amino acid such as lysine or histidine.

TABLE 9. Mulliken Partial Charges.



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